

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



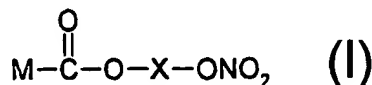
(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
WO 00/72838 A1

- (51) International Patent Classification⁷: A61K 31/04, 31/196, 31/33, A61P 1/04, 31/00
- (21) International Application Number: PCT/SE00/01071
- (22) International Filing Date: 25 May 2000 (25.05.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9902027-3 1 June 1999 (01.06.1999) SE
9904704-5 21 December 1999 (21.12.1999) SE
- (71) Applicant (for all designated States except US): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): EEK, Arne [SE/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE). RAUD, Johan [SE/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— With international search report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW USE OF COMPOUNDS AS ANTIBACTERIAL AGENTS



(57) Abstract: The present invention discloses a new use of NO-releasing NSAIDs, especially NO-releasing NSAIDs of formula (I), or a pharmaceutically acceptable salt or enantiomer thereof, for the manufacture of a medicament for the treatment of bacterial infections, especially caused or mediated by *Helicobacter pylori*. Disclosed is also the new use of a NO-releasing NSAID in combination with an acid susceptible proton pump inhibitor for the treatment of bacterial infections.

WO 00/72838 A1

NEW USE OF COMPOUNDS AS ANTIBACTERIAL AGENTS

Field of the invention

5 The present invention is directed to a new use of nitric oxide-releasing Non Steriodal Antiinflammatory Drugs (NO-releasing NSAIDs). More particularly the invention is directed to the use of NO-releasing NSAIDs for the manufacture of a medicament for the treatment of bacterial infections, paticularly caused or mediated by *Helicobacter pylori* as well as a combination with acid susceptible proton pump inhibitors for the treatment of
10 bacterial infections.

Background of the invention and prior art

NSAIDs, are among the most commonly prescribed and used drugs world^{WIDE}wide. Despite the
15 therapeutic benefits of NSAIDs, their use is limited. The use of NSAIDs may lead to gastric mucosal damage due to inhibited production of prostaglandins which increases the risk of gastrointestinal side-effects.

A recent proposal for reducing the side-effects associated with NSAIDs treatment is to use
20 nitric oxide-releasing NSAID derivatives (NO-releasing NSAIDs) (*del Soldato P et al., NO-releasing NSAID:s, A novel class of safer and effective antiinflammatory agents; Inflammopharmacology, 1996; 4; 181-188*). NO-releasing NSAIDs reduce the gastrointestinal side-effects but still have the pharmacological activity characteristic of the frequently used NSAIDs.

25 NO-releasing NSAIDs and pharmaceutically acceptable salts thereof are for instance described in WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641.

Helicobacter pylori is a gram-negative spirilliform bacteria which colonises in the gastric
30 mucosa. The relationship between gastrointestinal disorders and infections with

Helicobacter pylori proposed in 1983 by Warren (*Warren JR Lancet 1983;1.1273*) is well established today.

A number of different therapies have been proposed for the treatment of *Helicobacter pylori* infections. Combination therapies are commonly used. The most commonly used
5 comprise a proton pump inhibitor in combination with one or more antibacterial compounds such as claritromycin and amoxicillin. For instance WO93/00327 discloses the combination of a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH, and an acid degradable antibacterial compound. Some of
10 these therapies also comprise a bismuth compound, se for instance WO 98/03219 and WO98/22117, which latter application discloses a composition containing bismuth, an antimicrobial agent and a non-steriodal antiinflammatory agent for the treatment of gastrointestinal disorders caused or mediated by *Helicobacter pylori*.

15 In view of the vast number of the population suffering from gastrointestinal disorders caused or mediated by bacterial infections, such as *Helicobacter pylori* infections, and also in view of the fact that many bacterial strains develop a resistance to commonly used antibiotics, a continuing need exists for a safe and effective medicament having an antibacterial effect, especially for the treatment of *Helicobacter pylori* infections.

20

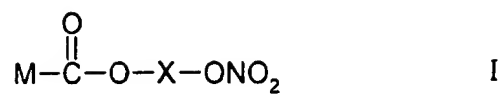
Outline of the invention

It has now surprisingly been found that NO-releasing NSAIDs have an antibacterial effect, which makes them useful for the treatment of bacterial infections.

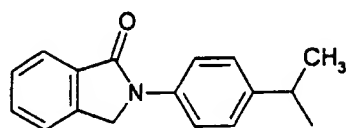
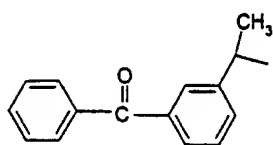
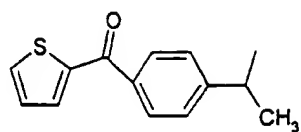
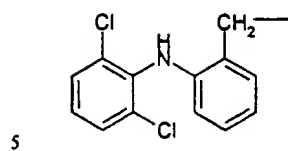
25

The present invention is related to the use of a NO-releasing NSAID as well as pharmaceutically acceptable salts or enantiomers thereof, for the manufacture of a medicament for the treatment of bacterial infections.

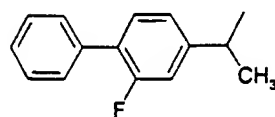
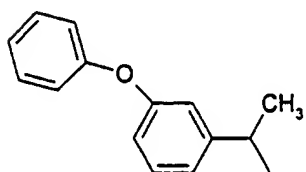
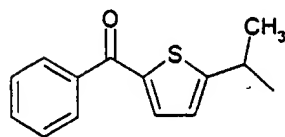
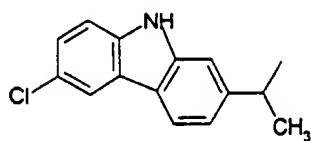
30 Preferably the NO-releasing NSAID is defined by the formula I



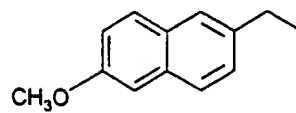
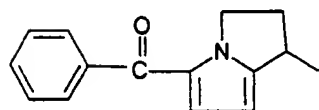
wherein M is selected from any one of

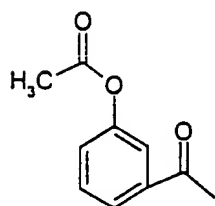
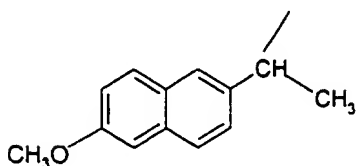
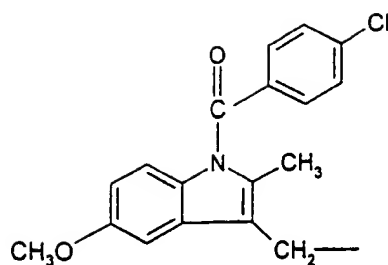
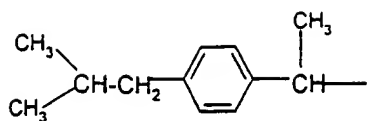


10



15





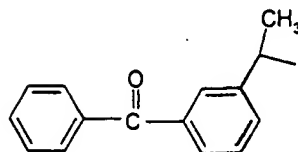
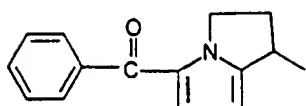
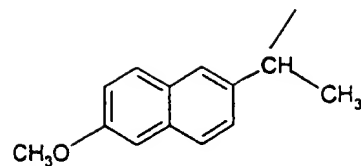
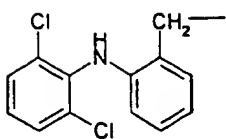
5

and X is a spacer, i.e. a compound forming a bridge between the nitrogen oxide donating group and the NSAID moiety, or a pharmaceutically acceptable salt or enantiomer thereof;

- 10 X is preferably selected from linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10; $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$.

M is not limited by the above definition but may be any other compound giving the
15 corresponding NSAID by hydrolysis of the compound according to formula I.

In a preferred embodiment of the invention M is selected from



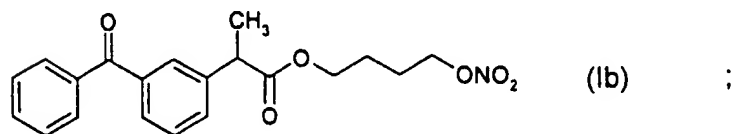
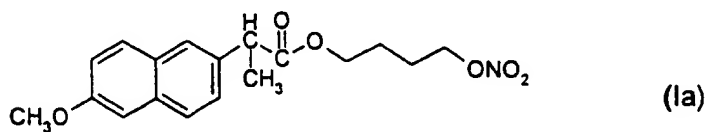
5

and X is selected from

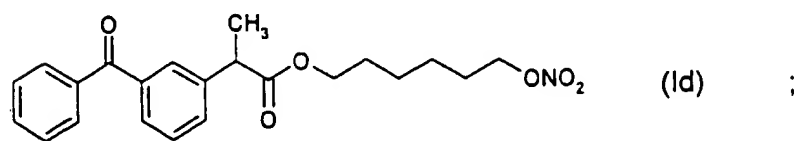
linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6;

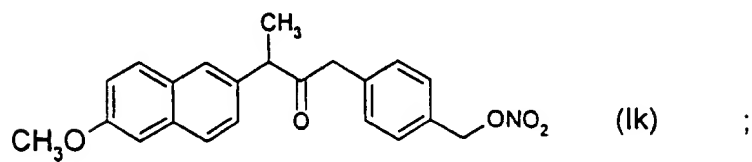
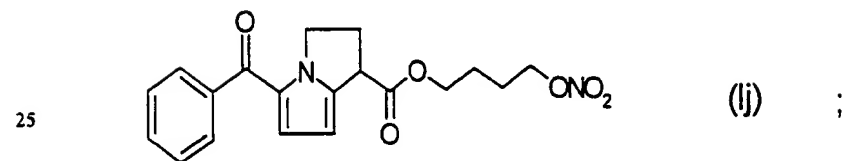
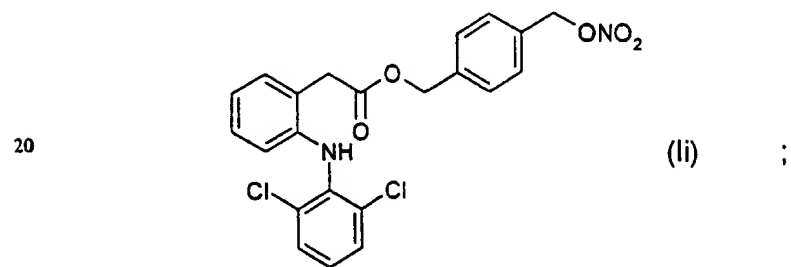
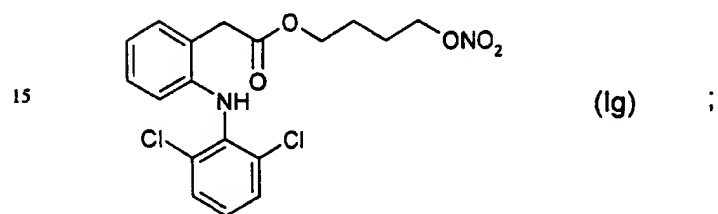
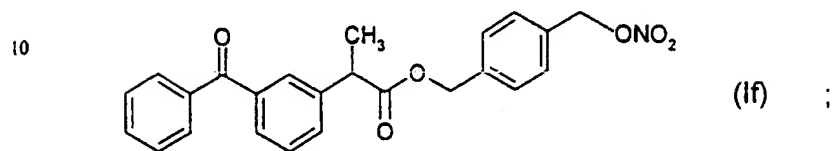
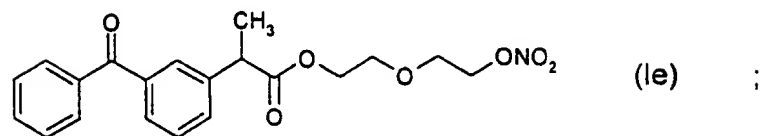
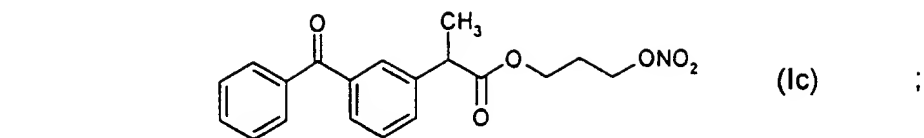
$-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

- 10 In an even more preferred embodiment of the invention the NO-releasing NSAID is a compound according to any one of the formulas

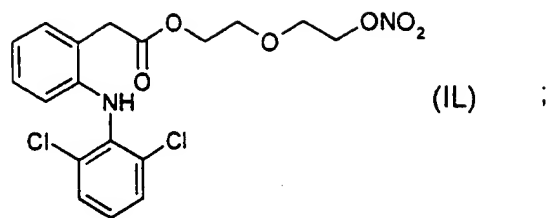


15

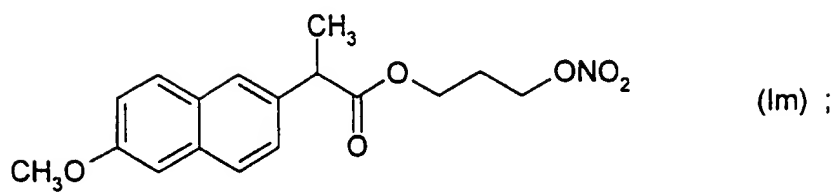




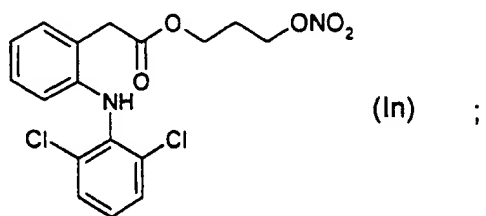
5



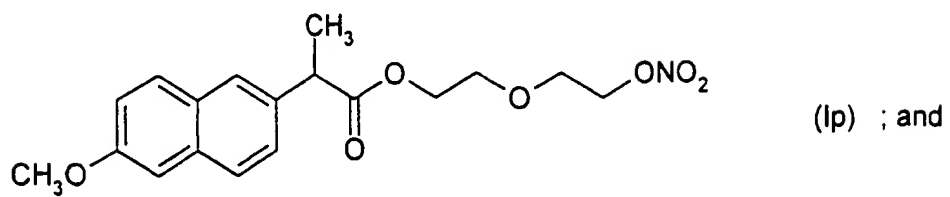
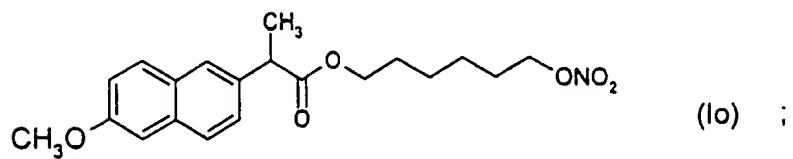
10

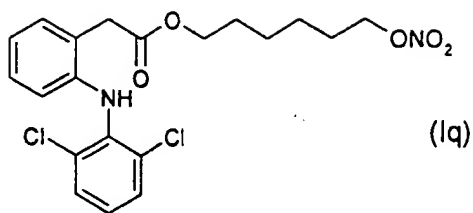


15



20





In a particularly preferred embodiment of the invention the NO-releasing NSAID is a compound according to formula Ia.

A further aspect of the invention is the use of a NO-releasing NSAID, preferably a compound of the formula I above, in the manufacture of a medicament for use in the treatment of *Helicobacter pylori* infections, especially in the treatment of gastrointestinal disorders caused or mediated by *Helicobacter pylori*.

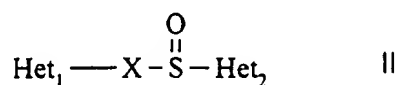
Still a further aspect of the invention is a method for the treatment of bacterial infections, in particular *Helicobacter pylori* infections, whereby an effective amount of a medicament comprising a NO-releasing NSAID, preferably a compound of the formula I, as active agent is administered to a subject suffering from said bacterial infection.

Also a pharmaceutical formulation suitable for use in the treatment of bacterial infections, which formulation comprising a NO-releasing NSAID, preferably a compound of the formula I, is within the scope of the invention.

Furthermore, the invention is related to the use of a NO-releasing NSAID, preferably a compound of the formula I, in combination with an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultaneous, separate or sequential administration in the treatment of bacterial infections, especially *Helicobacter pylori* infections.

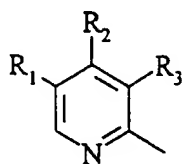
The invention may be applied in combination with other agents generally associated with treatment of bacterial infections, such as for instance antibacterial agents.

An acid susceptible proton pump inhibitor is, for instance, a compound of the general
 5 formula II

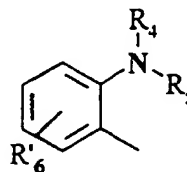


wherein

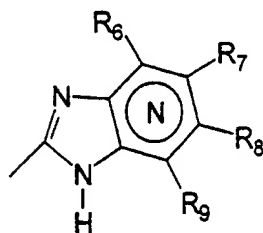
10 Het₁ is



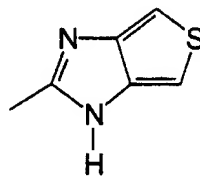
or



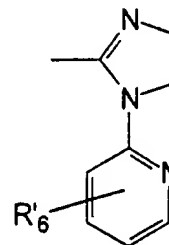
Het₂ is



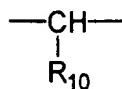
or



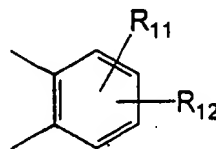
or



15 X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉
 20 optionally may be exchanged for a nitrogen atom without any substituents;

R_1 , R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

5 R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

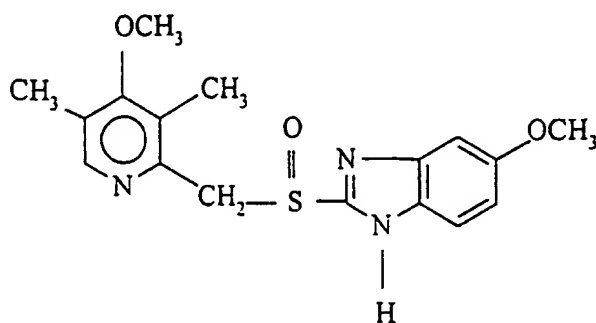
10 R_6 - R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6 - R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

15 R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof. The substituents may be branched or straight C_1 - C_9 -chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

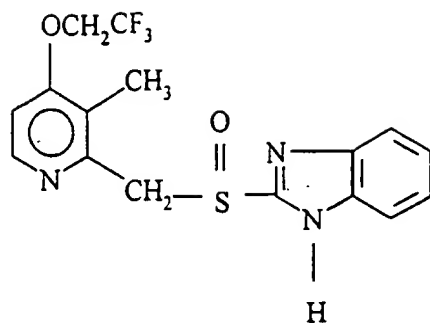
Examples of proton pump inhibitors according to formula II are

20



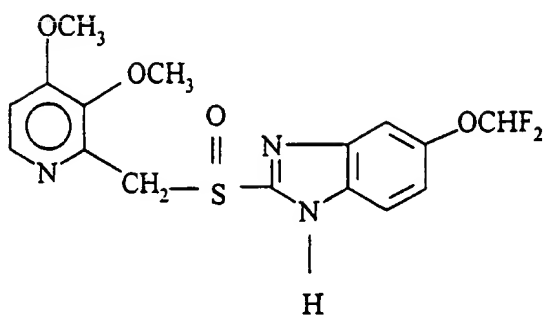
Omeprazole

25

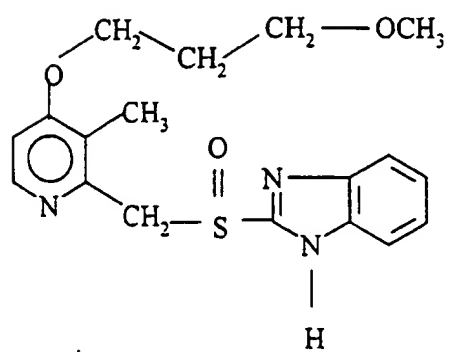


Lansoprazole

5

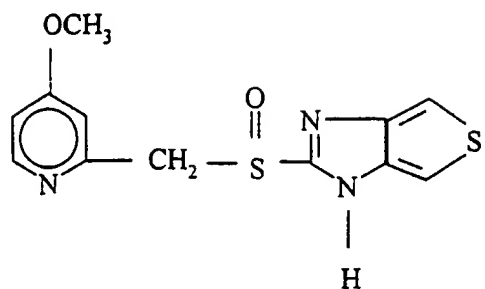
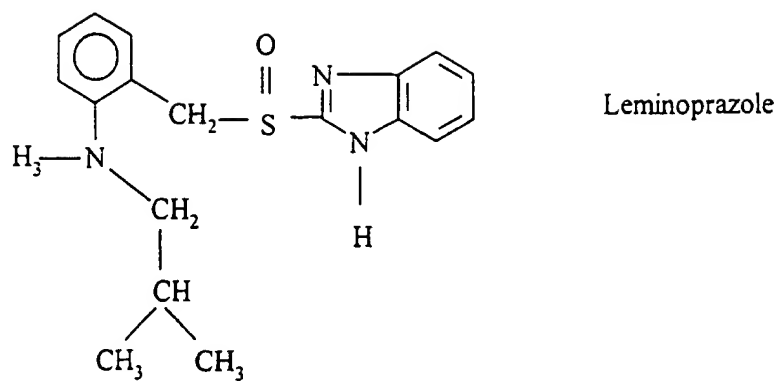


Pantoprazole

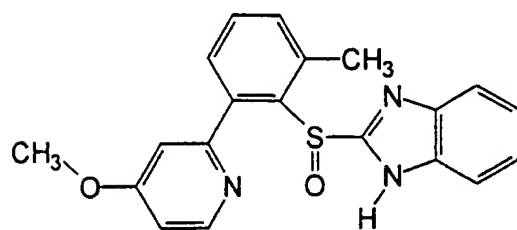
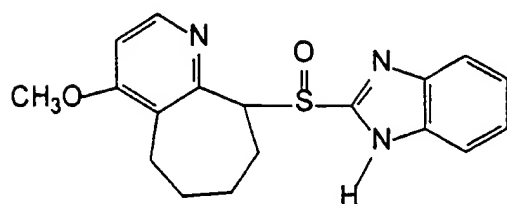


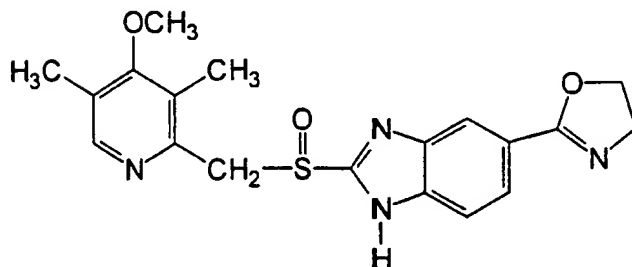
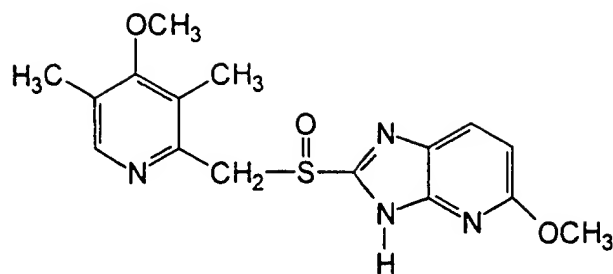
Pariprazole

10



5





5 The proton pump inhibitor may also be used in the form of a pharmaceutical acceptable salt or a single enantiomer in the claimed combination.

Preferably the proton pump inhibitor omeprazole, or an alkaline salt of omeprazole, such as the magnesium salt, or (S)-omeprazole or an alkaline salt of (S)-omeprazole, such as the
10 magnesium salt is used in the claimed combination.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, and further the especially suitable compounds are
15 described in WO95/01977 and WO94/27988.

According to the invention there is further provided a method for treating bacterial infections, particularly *Helicobacter Pylori* infections, which method comprises simultaneous, separate or sequential administration to a subject suffering from a bacterial
20 infection one or more pharmaceutical formulations comprising a NO-releasing NSAID, preferably a compound according to the formula I, and an acid susceptible proton pump

inhibitor. Also pharmaceutical formulations for simultaneous, separate or sequential administration to be used in the treatment of bacterial infections, which formulations comprise an NO-releasing NSAID, preferably a compound of the formula I and an acid susceptible proton pump inhibitor are within the scope of the invention.

5

The NO-releasing NSAID alone or in combination with an acid susceptible compound may be in a dosage form administered orally, rectally, epidurally, intravenously, intramuscularly, subcutaneously, by infusion, nasally or any other way suitable for administration. Preferably the active compound(-s) is administered orally.

10

The active compound(-s) are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active compound(-s) varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0.5 – 5000 mg, preferably 5 – 1000 mg, of the NO-releasing NSAID. If a combination with a proton pump inhibitor is used 0.5 – 5000 mg of the NO-releasing NSAID, and 0.1 – 200 mg of the proton pump inhibitor will be comprised in each dosage form, or in two separate dosage forms. Preferably, the amount of the NO-releasing NSAID in each dosage form is 5 – 1000 mg, and the amount of the proton pump inhibitor 10 - 80 mg.

20

Detailed description of the invention

The invention is described in more detail by the following non-limiting examples.

25

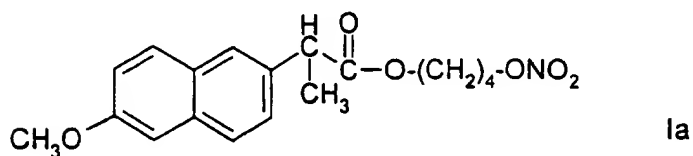
The examples below support that NO-releasing NSAIDs are active against *Helicobacter pylori*, and that the antibacterial activity is concentration dependent.

30

Example 1.

Strain: *Helicobacter pylori* reference strain NCTC 11 637 (National Type Culture Collection, from Smittskyddsinstitutet in Solna, Sweden), an antibiotic
5 sensitive reference strain

Substance:

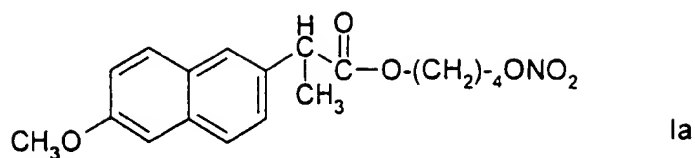


- 10 *Helicobacter pylori* was grown on blood agar plates, having a diameter of 90 mm, for three days under microaerophilic conditions at 37°C. The bacteria were suspended in PBS (phosphate buffer saline) to approximately 10^8 cfu/ml. Approximately 2 ml of the suspension was added to one agar plate and spread even on the surface of the agar. Overflow was removed with a syringe. Wells, like small holes, 3 mm in diameter, were
15 made in the agarplate by removing agar. Three wells per plate were made.
- A stock solution of a compound of the formula Ia having the concentration 100 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.
- Result: The inhibition zone around each well was large, i.e. it was not possible to measure
20 the diameter of the zone.

Example 2.

- Strain: *Helicobacter pylori* reference strain NCTC 11 637 (see Example 1), an
25 antibiotic sensitive reference strain

Substance:



The plates with the wells were prepared according to Example 1.

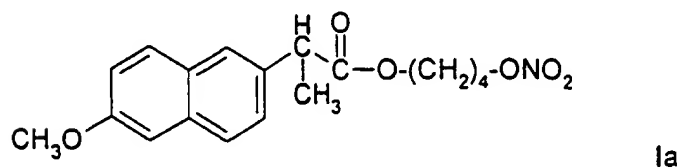
- 5 A stock solution of a compound of the formula Ia having the concentration 10 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around each well was large, i.e. it was not possible to measure
10 the diameter of the zone.

Example 3.

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive
15 reference strain (see Example 1)

Substance:



- 20 The plates with the wells were prepared according to Example 1.

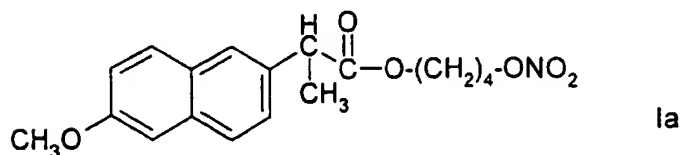
A stock solution of a compound of the formula Ia having the concentration 1 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

- 25 Result: The inhibition zone around each well was 13 mm.

Example 4.

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

5 Substance:



The plates with the wells were prepared according to Example 1.

10

A stock solution of a compound of the formula Ia having the concentration 100 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

15 Result: The inhibition zone around each well was 10.4 mm.

Comparative testsExample A

20

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

25 The plates with the wells were prepared according to Example 1.

A stock solution of Naproxen having the concentration 10 000 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around the each well was 16.6 mm.

5

Example B

10 Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

15

A stock solution of Naproxen having the concentration 1000 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

20 Result: No inhibition zones around the wells were formed.

Example C

25 Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

30 A stock solution of Naproxen having the concentration 100 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

5

Example D

10 Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: S-nitroso-N-acetyl-penicillamin (SNAP)

The plates with the wells were prepared according to Example 1.

15

A stock solution of SNAP with the concentration 10 000 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

20 Result: No inhibition zones around the wells were formed.

Example E

25 Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Di-methyl-sulphate-oxide (DMSO)

The plates with the wells were prepared according to Example 1.

30 A solution of DMSO alone with the concentration 20 µg/ml was prepared.

30 μ l of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

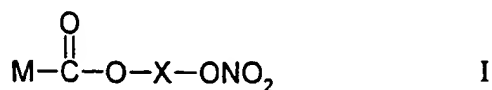
Result: No inhibition zones around the wells were formed.

Claims

1. Use of a NO-releasing NSAID as well as a pharmaceutically acceptable salt or an enantiomer thereof, for the manufacture of a medicament for the treatment of bacterial
5 infections.

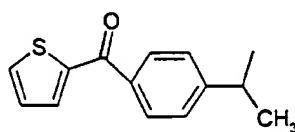
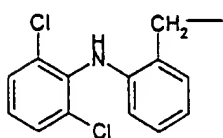
2. Use of a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultaneous, separate, or sequential
10 administration in the treatment of bacterial infections.

3 Use according to claim 1 or 2 wherein the NO-releasing NSAID is a compound of the formula I

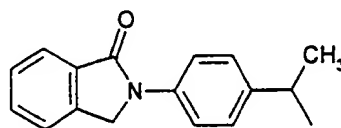
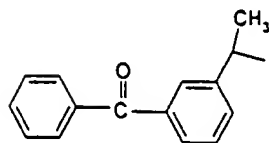


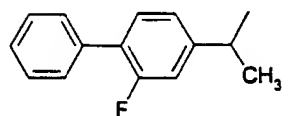
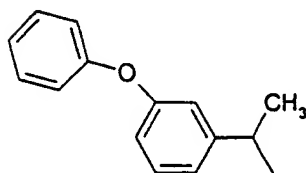
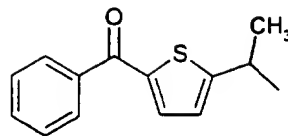
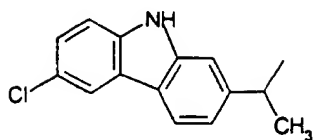
15

wherein M is selected from anyone of

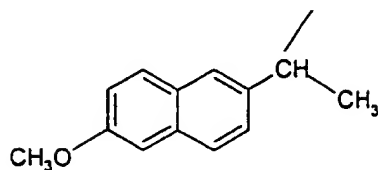
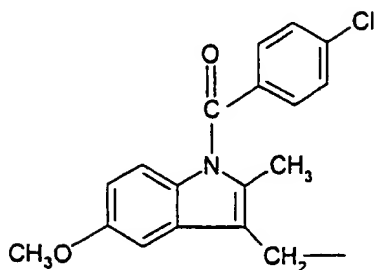
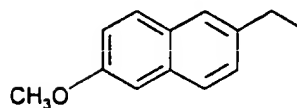
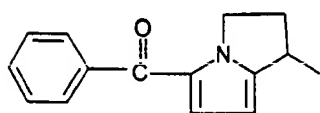


20

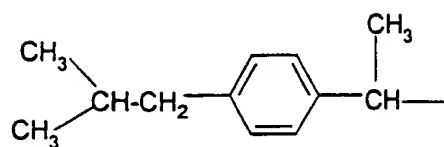
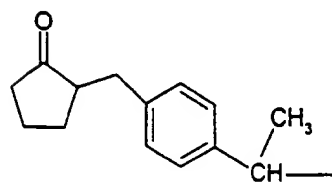




5



10



15

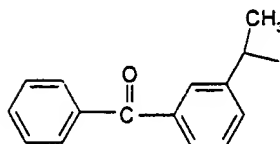
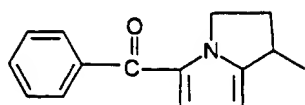
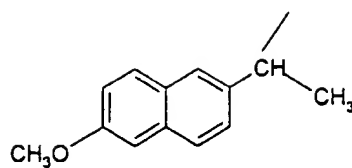
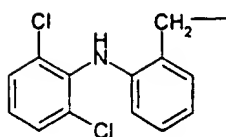
and X is selected from

linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$,

or a pharmaceutically acceptable salt or enantiomer thereof.

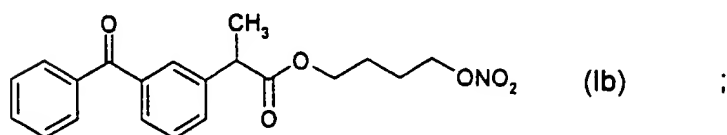
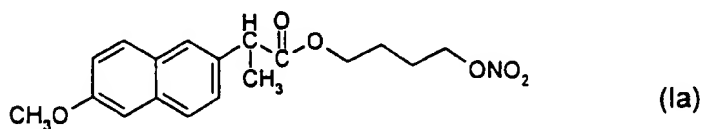
4. Use according to claim 3 wherein M in formula I is selected from



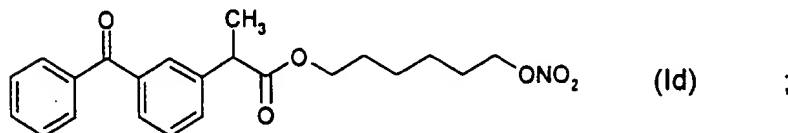
5

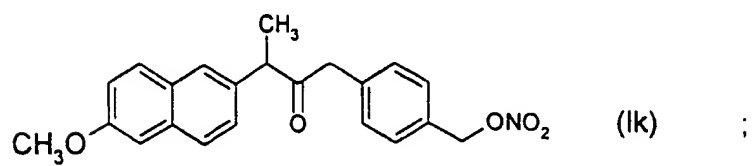
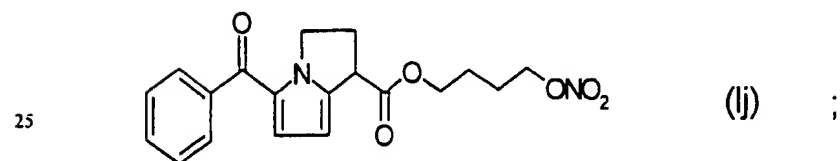
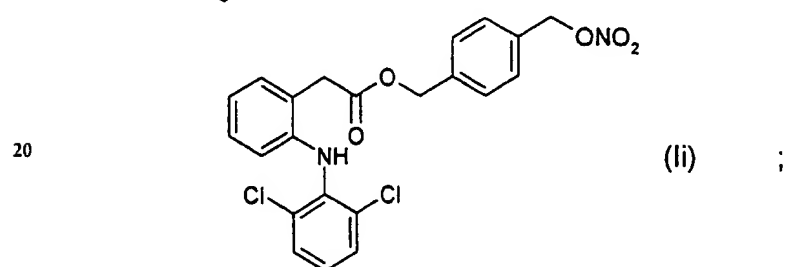
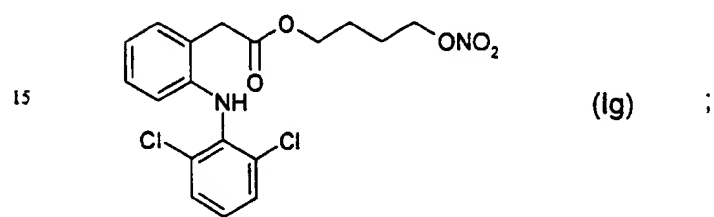
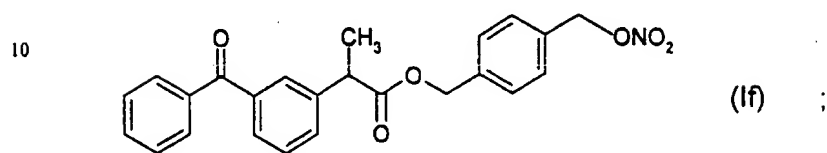
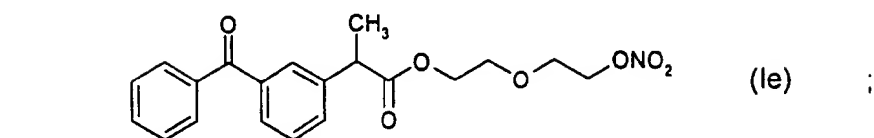
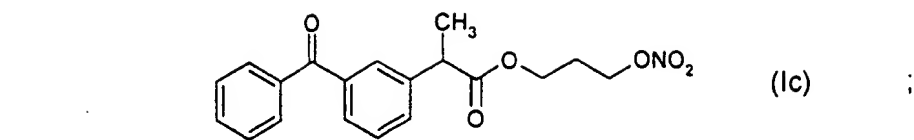
5. Use according to claim 3 or 4 wherein X in formula I is selected from linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6, $-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

10 6. Use according to any one of claims 1 - 3 wherein the NO-releasing NSAID is a compound according to any one of the formulas Ia - Iq

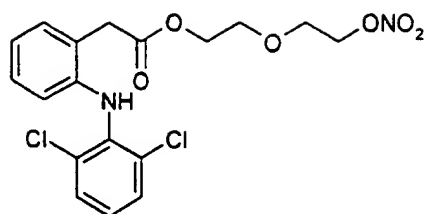


15



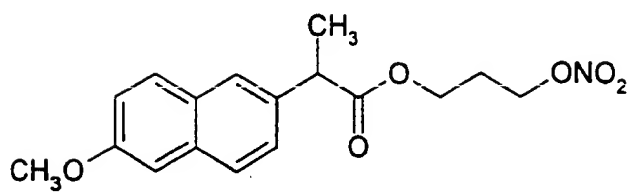


5



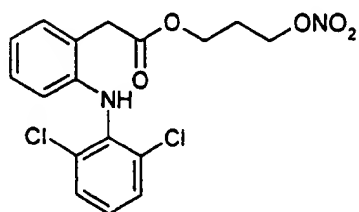
(IL) ;

10

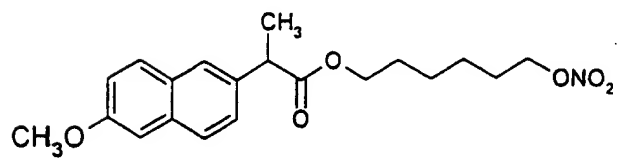


(Im) ;

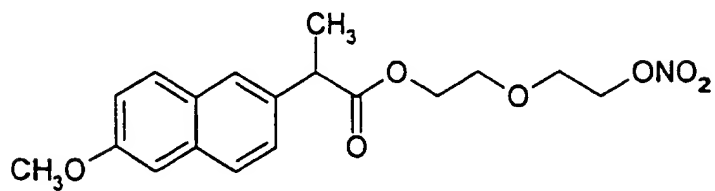
15



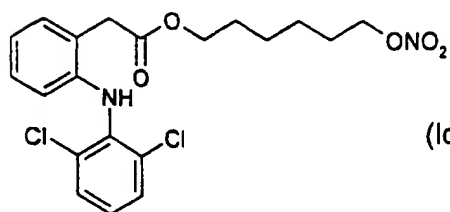
(In) ;



(Io) ;

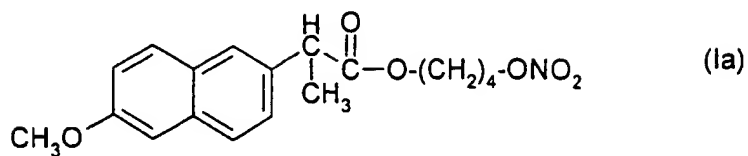


(Ip) ; and



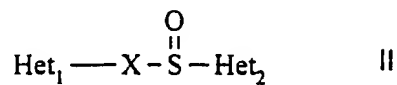
(Iq)

7. Use according to claim 6, wherein the NO-releasing NSAID is a compound of formula Ia



8. Use according to claim 2 wherein the acid susceptible proton pump inhibitor is a compound of the formula II

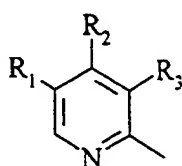
10



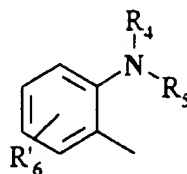
wherein

Het₁ is

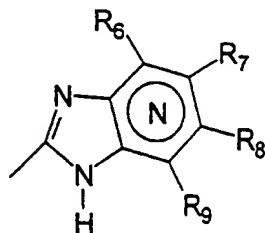
15



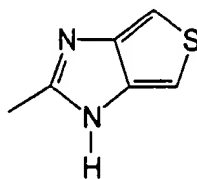
or



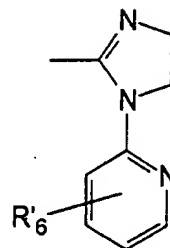
Het₂ is



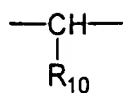
or



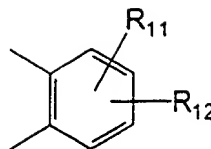
or



X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉
 5 optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy
 optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino,
 morpholino, halogen, phenyl and phenylalkoxy;

10

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

R₆' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

15 R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-
 alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉
 form ring structures which may be further substituted;

R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

20

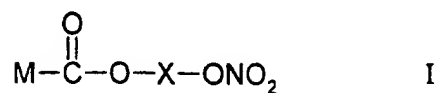
R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl, alkyl
 groups, alkoxy groups and moities thereof, they may be branched or straight C₁ - C₉ -
 chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

25 9. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is
 selected from omeprazole, an alkaline salt thereof, (S)-omeprazole and an alkaline salt
 thereof.

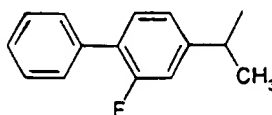
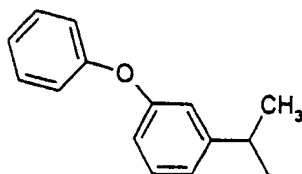
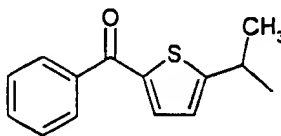
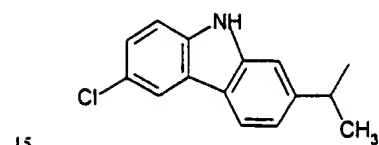
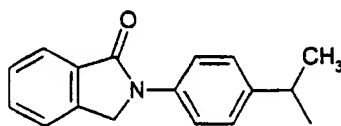
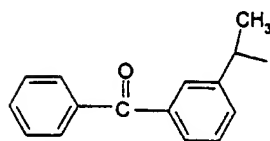
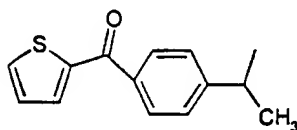
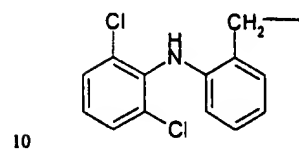
10. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is lansoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.
- 5 11. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is pantoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.
12. Use according to any one of the preceeding claims 1 to 11, wherein the bacterial
10 infection is caused or mediated by *Helicobacter pylori*.
13. Use according to claim 1, wherein the amount of NO-releasing NSAID in each dosage form is 0.5 – 5000 mg.
- 15 14. Use according to claim 13, wherein the amount of NO-releasing NSAID is 5 – 1000 mg.
15. Use according to claim 2, wherein the amount of NO-releasing NSAID is 0.5 – 5000 mg and the amount of proton pump inhibitor is 0.1 – 200 mg together in one dosage
20 form or in two separate dosage forms.
16. Use according to claim 15, wherein the amount of NO-releasing NSAID is 5 – 1000 mg and the amount of proton pump inhibitor is 10 – 80 mg.
- 25 17. A method for the treatment of a bacterial infection, comprising administering to a patient suffering from said bacterial infection, an effective amount of a NO-releasing NSAID or a pharmaceutically acceptable salt or an enantiomer thereof.
18. A method for the treatment of a bacterial infection, comprising simultaneously,
30 separately or sequentially administration to a patient suffering from said bacterial infection,

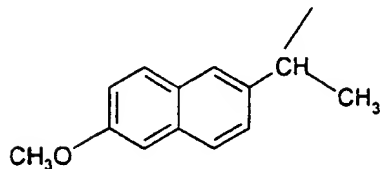
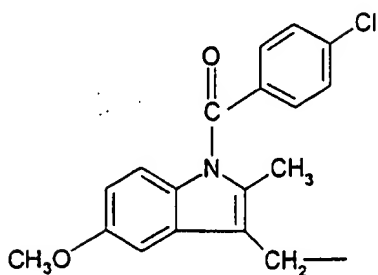
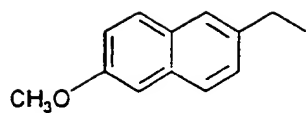
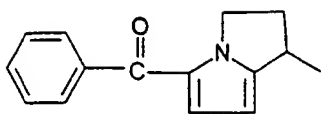
an effective amount of a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer.

19. A method according to claim 17 or 18 wherein the NO-releasing NSAID is a
5 compound of the formula I

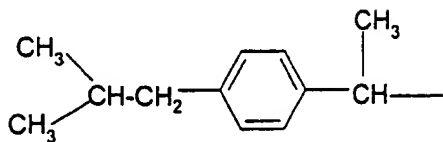


wherein M is selected from





5

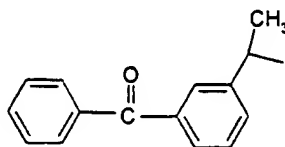
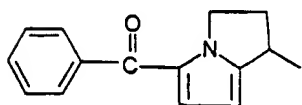
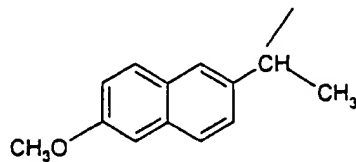
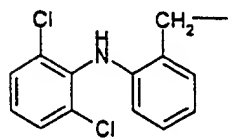


and X is selected from

- 10 linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;
 $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$,

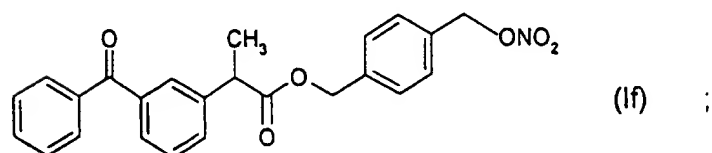
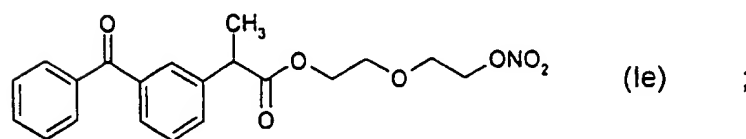
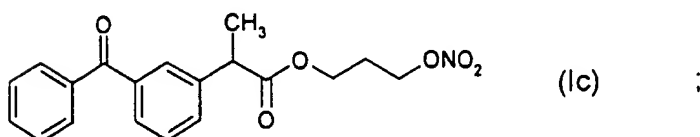
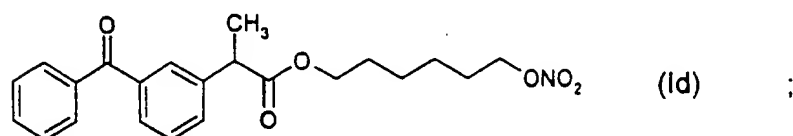
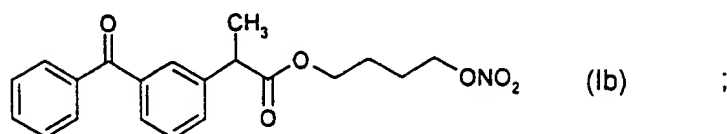
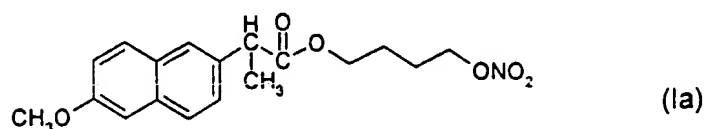
or a pharmaceutically acceptable salt or enantiomer thereof.

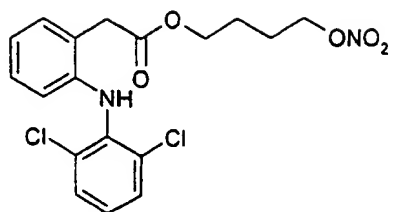
- 15 20. A method according to claim 19 wherein M in formula I is selected from



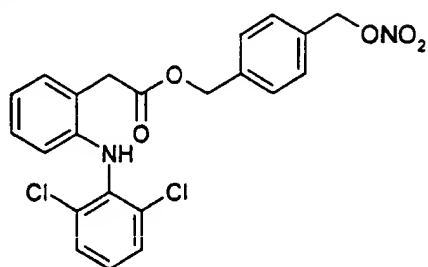
21. A method according to claim 19 or 20 wherein X in formula I is selected from linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6, $-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

22. A method according to any one of claim 17 – 19, wherein the NO-releasing NSAID is a compound according to any one of the formulas Ia - Iq

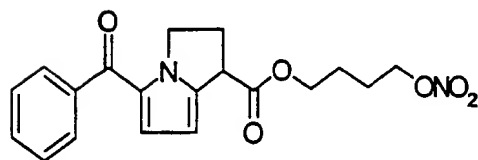




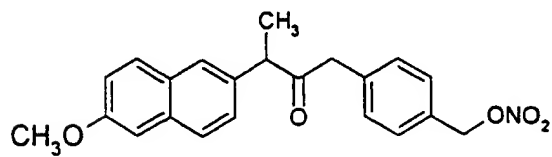
(Ig) ;



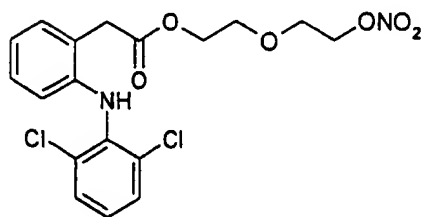
(Ii) ;



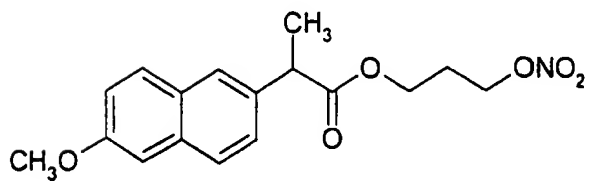
(Ij) ;



(Ik) ;

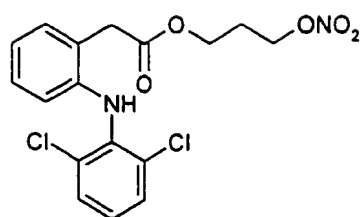


(Il) ;

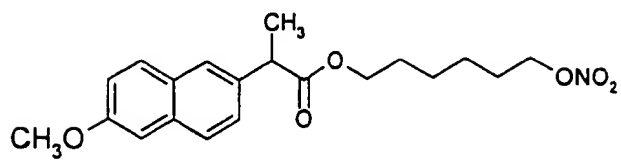


(Im) ;

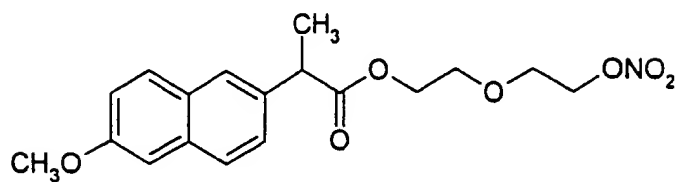
5



(In) ;

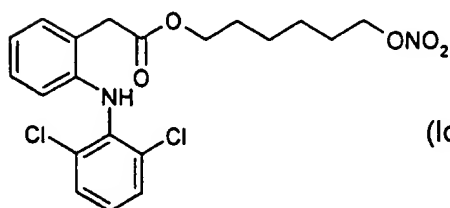


(Io) ;



(Ip) ; and

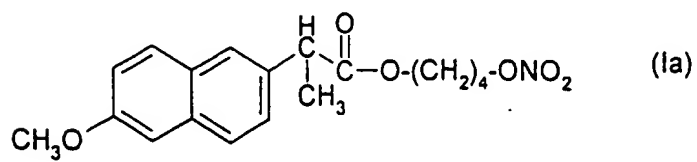
10



(Iq)

15

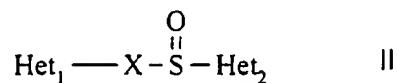
23. A method according to claim 22, wherein the NO-releasing NSAID is a compound of formula Ia



(Ia)

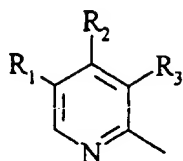
20

24. A method according to claim 18 wherein the acid susceptible proton pump inhibitor is a compound of the formula II

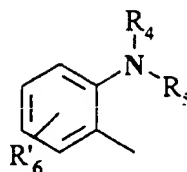


5 wherein

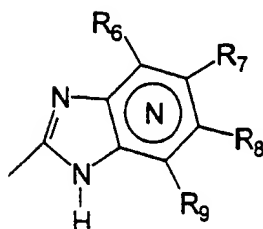
Het₁ is



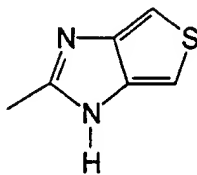
or



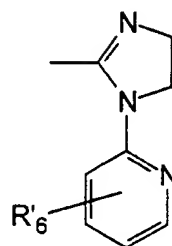
10 Het₂ is



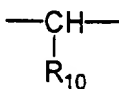
or



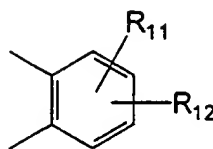
or



X =



or



wherein

15

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy
 20 optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

R₆' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

5

R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

10 R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moieties thereof, they may be branched or straight C₁ - C₉ - chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

15

25. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt thereof, (S)-omeprazole and an alkaline salt thereof.

20 26. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is lansoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

27. A method according to claim 24 wherein the acid susceptible proton pump inhibitor
25 is pantoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

28. A method according to any one of the preceeding claims 17 to 27, wherein the bacterial infection is caused or mediated by *Helicobacter pylori*.

30

29. A method according to claim 17, wherein the amount of NO-releasing NSAID in each dosage form is 0.5 – 5000 mg.

30. A method according to claim 29, wherein the amount of NO-releasing NSAID is
5 5 – 1000 mg.

31. A method according to claim 18, wherein the amount of NO-releasing NSAID is 0.5 – 5000 mg and the amount of proton pump inhibitor is 0.1 – 200 mg together in one dosage form or in two separate dosage forms.

10

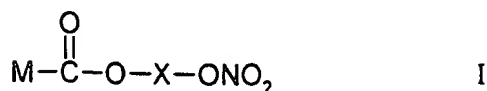
32. A method according to claim 31, wherein the amount of NO-releasing NSAID is 5 – 1000 mg and the amount of proton pump inhibitor is 10 – 80 mg.

33. A pharmaceutical formulation suitable for use in the treatment of bacterial
15 infections, comprising a NO-releasing NSAID or a pharmaceutically acceptable salt or an enantiomer thereof as active agent.

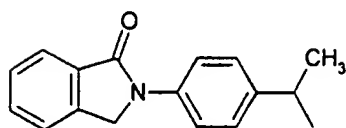
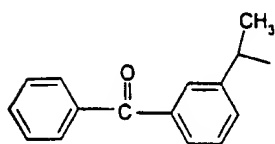
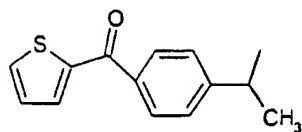
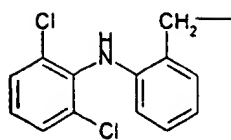
34. A pharmaceutical formulation suitable for use in the treatment of bacterial infections, comprising a NO-releasing NSAID and an acid susceptible proton pump
20 inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer as active agents.

35. A pharmaceutical formulation according to claim 25 or 26 wherein the NO-releasing NSAID is a compound of the formula I

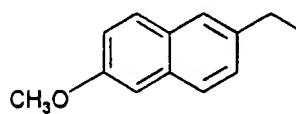
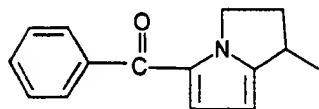
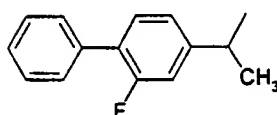
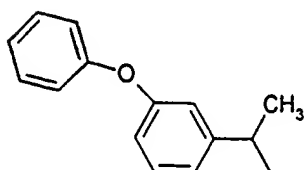
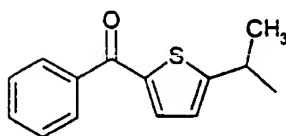
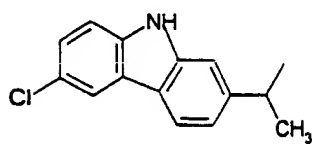
25



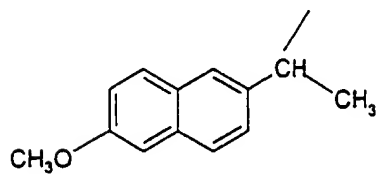
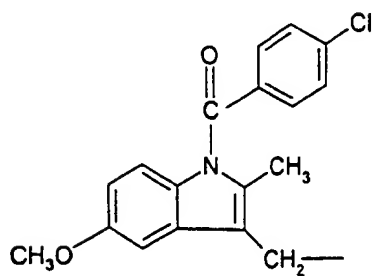
wherein M is selected from



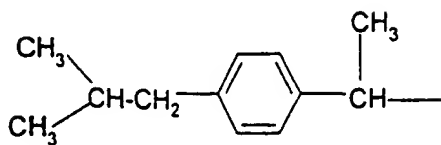
5



10



15



and X is selected from

linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$;

5

or a pharmaceutically acceptable salt or enantiomer thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/01071

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/04, A61K 31/196, A61K 31/33, A61P 1/04, A61P 31/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1999:500417, Document no. 131:255524, Yanaka, Akinori: "Role of nitric oxide in the pathogenesis of gastrointestinal diseases"; & Ensho (1999), 19 (3), 129-135 --	1-32
X	Pharmacol Ther, Volume 11, 1997, N.M. DAVIES et al, "NO-naproxen vs. naproxen: ulcerogenic, analgesic and anti-inflammatory effects" page 69 - page 79 --	1-32
X	WO 9967210 A1 (DUKE UNIVERSITY MEDICAL CENTER), 29 December 1999 (29.12.99), see part. page 3, line 18-19, page 15, line 17-20 --	1-32



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

18 Sept 2000

Date of mailing of the international search report

20 -09- 2000

Name and mailing address of the ISA/

Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Authorized officer

Eva Johansson/GH

Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/01071

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9509612 A1 (ENTREMED, INC. ET AL), 13 April 1995 (13.04.95), see part. page 8, line 26, page 9, line 3 and 7 --	1-32
X	WO 9404484 A1 (CORLAY S.L. ET AL), 3 March 1994 (03.03.94) --	33-35
X	WO 9509831 A1 (NICOX LIMITED), 13 April 1995 (13.04.95) --	33-35
X	WO 9412463 A1 (HCT-HEALTH CARE TRADING LTD.), 9 June 1994 (09.06.94) --	33-35
X	WO 9530641 A1 (NICOX LIMITED), 16 November 1995 (16.11.95) --	33-35
A	WO 9731654 A1 (NICOX S.A.), 4 Sept 1997 (04.09.97) --	1-35
A	WO 9822117 A1 (THE PROCTER & GAMBLE COMPANY), 28 May 1998 (28.05.98) --	1-35
A	Am J Med, Volume 104, No 3A, 1998, Adrian Schmassmann, "Mechanisms of Ulcer Healing and Effects of Nonsteroidal Anti-inflammatory Drugs" page 43S - page 51S --	1-35
A	Aliment Pharmacol Ther, Volume 13, 1999, S. FIORUCCI et al, "Nitric oxide-releasing NSAIDs inhibit interleukin-1.β. converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNF.α." page 421 - page 435 -- -----	1-35

INTERNATIONAL SEARCH REPORT

on on patent family members

01/08/00

International application No.

PCT/SE 00/01071

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9967210	A1	29/12/99	AU	4580599 A	10/01/00
WO	9509612	A1	13/04/95	AU	7972294 A	01/05/95
				US	5814666 A	29/09/98
WO	9404484	A1	03/03/94	AT	143941 T	15/10/96
				CA	2120942 A	03/03/94
				DE	69305322 D,T	20/02/97
				DK	609415 T	18/11/96
				EP	0609415 A,B	10/08/94
				SE	0609415 T3	
				ES	2093979 T	01/01/97
				GR	3021404 T	31/01/97
				HK	1006967 A	00/00/00
				IT	1256345 B	01/12/95
				IT	MI922006 D	00/00/00
				JP	7500355 T	12/01/95
				RU	2109009 C	20/04/98
				US	5597847 A	28/01/97

INTERNATIONAL SEARCH REPORT

on on patent family members

International application No.

01/08/00

PCT/SE 00/01071

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
WO	9509831	A1	13/04/95	AT 168986 T	15/08/98
				AU 678063 B	15/05/97
				AU 7809294 A	01/05/95
				BR 9407749 A	12/02/97
				CA 2173582 A	13/04/95
				DE 69412109 D,T	21/01/99
				EP 0722434 A,B	24/07/96
				SE 0722434 T3	
				ES 2120070 T	16/10/98
				GB 2283238 A,B	03/05/95
				HK 1004916 A	00/00/00
				HU 74446 A	30/12/96
				HU 9600874 D	00/00/00
				JP 9503214 T	31/03/97
				RU 2136653 C	10/09/99
				SI 722434 T	00/00/00
				US 5700947 A	23/12/97
				US 5780495 A	14/07/98
				AT 184589 T	15/10/99
				AU 702662 B	25/02/99
				AU 2215695 A	29/11/95
				BR 9507634 A	23/09/97
				CA 2190087 A	16/11/95
				DE 69512232 D,T	24/02/00
				EP 0759899 A,B	05/03/97
				SE 0759899 T3	
				ES 2139199 T	01/02/00
				HU 75961 A	28/05/97
				HU 9603107 D	00/00/00
				IL 113255 D	00/00/00
				IT 1269735 B	15/04/97
				IT MI940916 D	00/00/00
				JP 9512798 T	22/12/97
				SI 759899 T	00/00/00
				US 5861426 A	19/01/99
				WO 9530641 A	16/11/95

INTERNATIONAL SEARCH REPORT

on on patent family members

01/08/00

International application No.

PCT/SE 00/01071

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9412463	A1	09/06/94	AT	152092 T	15/05/97
				AU	676527 B	13/03/97
				AU	5624194 A	22/06/94
				BR	9307530 A	25/05/99
				CA	2150229 A	09/06/94
				DE	69310204 D, T	20/11/97
				DK	670825 T	13/10/97
				EP	0670825 A, B	13/09/95
				SE	0670825 T3	
				ES	2103563 T	16/09/97
				GR	3024018 T	31/10/97
				HU	73773 A	30/09/96
				HU	9501531 D	00/00/00
				IT	1256450 B	05/12/95
				IT	MI922699 D	00/00/00
				JP	8504191 T	07/05/96
				RU	2127723 C	20/03/99
				US	5621000 A	15/04/97
WO	9530641	A1	16/11/95	AT	168986 T	15/08/98
				AT	184589 T	15/10/99
				AU	678063 B	15/05/97
				AU	702662 B	25/02/99
				AU	2215695 A	29/11/95
				AU	7809294 A	01/05/95
				BR	9407749 A	12/02/97
				BR	9507634 A	23/09/97
				CA	2173582 A	13/04/95
				CA	2190087 A	16/11/95
				DE	69412109 D, T	21/01/99
				DE	69512232 D, T	24/02/00
				EP	0722434 A, B	24/07/96
				SE	0722434 T3	
				EP	0759899 A, B	05/03/97
				SE	0759899 T3	
				ES	2120070 T	16/10/98
				ES	2139199 T	01/02/00
				HU	74446 A	30/12/96
				HU	75961 A	28/05/97
				HU	9600874 D	00/00/00
				HU	9603107 D	00/00/00
				IL	113255 D	00/00/00
				IT	1269735 B	15/04/97
				IT	MI940916 D	00/00/00
				JP	9503214 T	31/03/97
				JP	9512798 T	22/12/97
				RU	2136653 C	10/09/99
				SI	722434 T	00/00/00
				SI	759899 T	00/00/00
				US	5700947 A	23/12/97
				US	5780495 A	14/07/98
				US	5861426 A	19/01/99
				WO	9509831 A	13/04/95
				IT	1274609 B	18/07/97
				IT	MI941731 D	00/00/00

INTERNATIONAL SEARCH REPORT

on patent family members

01/08/00

International application No.

PCT/SE 00/01071

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9731654	A1	04/09/97	AU	706591 B	17/06/99
				AU	2092497 A	16/09/97
				BR	9707739 A	27/07/99
				CA	2247848 A	04/09/97
				EP	0904110 A	31/03/99
				HU	9900993 A	28/09/99
				IT	1282686 B	31/03/98
				IT	MI960352 A,U	26/08/97
				JP	2000506133 T	23/05/00
WO	9822117	A1	28/05/98	EP	0941101 A	15/09/99
				NO	992469 A	22/07/99